

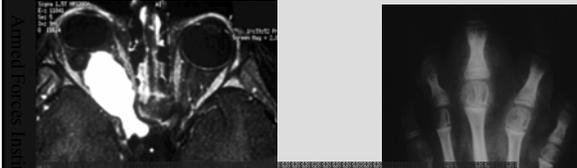
Armed Forces Institute of Pathology

Neurofibromatosis Head to Toe with Pathologic Correlation

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Illustrations by Aletta A. Frazier, M.D.



RSNA 2007 Special Focus
 Neurofibromatosis Head to Toe
 Pathologic Correlation

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Dorland's Medical Dictionary

the matter into a cytotome, with invagination of the matter by the cell membrane to form a food vacuole, a process of food intake occurring in ciliate protozoa.

phagocyte (fag'o-sit) phage type; see under type.

phakitis (fa-ki'tis) [Gr. *phakos* lens + *-itis*] inflammation of the crystalline lens.

phako- [Gr. *phakos* lentil, or lentil-shaped object, a spot on the body, a freckle, or wart] beginning thus, see also those beginning: phaco-

phakoma (fah-ko'mah) | *phaco-* + *-oma* 1. an occasional small, grayish white tumor seen microscopically in the retina in tuberous sclerosis. 2. a patch of myelinated nerve fibers seen very infrequently in the retina in neurofibromatosis.

phakomatosis (fak'o-mah-to'sis), pl. *phakomatoses* [Gr. *phakos* mother spot] an ophthalmologic term for any of four hereditary syndromes (neurofibromatosis, tuberous sclerosis, encephalotrigeminal angiomatosis, and cerebretinal angiomatosis) characterized by disseminated hamartomas of the eye, skin, and brain.

phalacroisis (fal'ah-kro'sis) [Gr. *phalakros* baldness] alopecia.

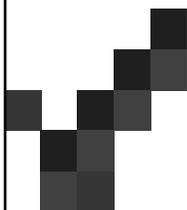
phalangeal (fal-lan'je-al) pertaining to a phalanx.

phalangeotomy (fal'an-jek'to-me) excision of a phalanx of a finger or toe.

Phakomatoses.

Neuro-Cutaneous Syndromes

- Systemic disorders
- Prominent and Diagnostic Stigmata
- Most Inherited as Autosomal Dominant
 - NF-1
 - NF-2
 - Tuberous Sclerosis
 - von Hippel-Lindau



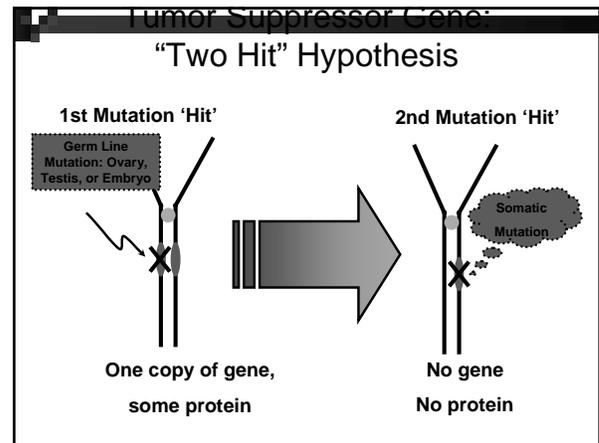
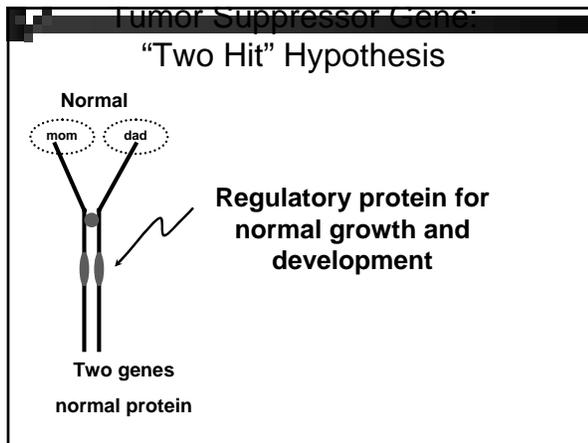
Molecular Biology

Mutations
 and the
 Genetic "Two Hit Theory"

Genes and Proteins

	Gene	Protein	aa	kD	Alternate names
NF1	17q11.2	neurofibromin (pNF)	2838	250	
NF2	22q12.2	neurofibromin 2 (pNF2)	595 - 614	69	Schwannomin, Merlin
TSC1	9q34	hamartin	1164		
TSC2	16p13.3	tuberin	1807	200	
VHL	3p26-p25	VBP1 30	213	28-30	pVHL 19

<http://www.ncbi.nlm.nih.gov/UniGene/>



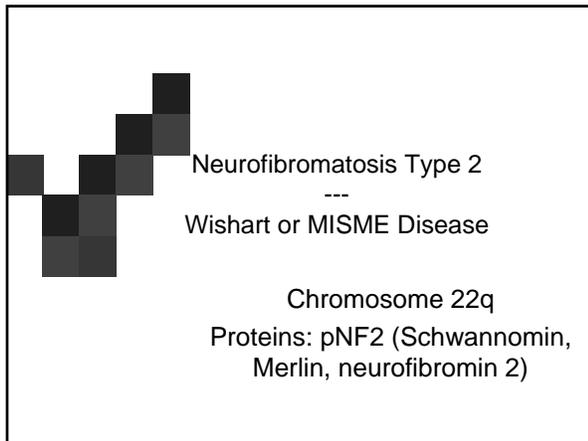
Neurofibromatosis Type 1
Chromosome 17q

vs.

Neurofibromatosis Type 2
Chromosome 22q

- NEUROFIBROMATOSIS**
- NF-1, von Recklinghausen
 - ("peripheral" – bad term)
 - NF-2, Bilateral Acoustic
 - ("central" – bad term)
 - NF-3, Overlap of 1 and 2
 - NF-5, Segmental (e.g. a quadrant)
 - NF-6, Cafe-au-lait, w/o CNS/PNS
 - NF-7, Late Onset
 - NF-8, Other

- NEUROFIBROMATOSIS**
- **Neurofibromatosis Type 1 (NF-1)**
 - von Recklinghausen Disease
 - "True" Neurofibromatosis
 - Prominent Cutaneous Signs
 - Chromosome 17q
 - **Neurofibromatosis Type 2 (NF-2)**
 - Bilateral Acoustic Schwannoma
 - "Central Neurofibromatosis"
 - Minimal Skin Manifestations
 - Chromosome 22q



NEUROFIBROMATOSES

- **Neurofibromatosis Type 1 (NF-1)**
 - von Recklinghausen Disease
 - "True" Neurofibromatosis
 - Prominent Cutaneous Signs
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 - Bilateral Acoustic Schwannoma
 - "Central Neurofibromatosis"
 - Minimal Skin Manifestations
 - Chromosome 22q

NEUROFIBROMATOSIS - Type 2

- Incidence: 1/50,000
- Inheritance: Autosomal Dominant
- Age at Presentation: Birth to 40's (peak in 20's)
- Sx at Presentation: Hearing loss from VS
- Diagnostic Criteria: VIII masses
- Chromosome Abnl.: 22
- Cutaneous Findings: minimal (skin tags)
- CNS Findings: Schwannoma, Meningioma, Ependymoma (intramedullary spinal cord)

CNS Neoplasms - Chromosome Loss of Heterozygosity

- Schwannoma - 22q
- Meningioma - 22q (long arm)
- Ependymoma - 22

} NF-2

NOT Neurofibroma } NF-1

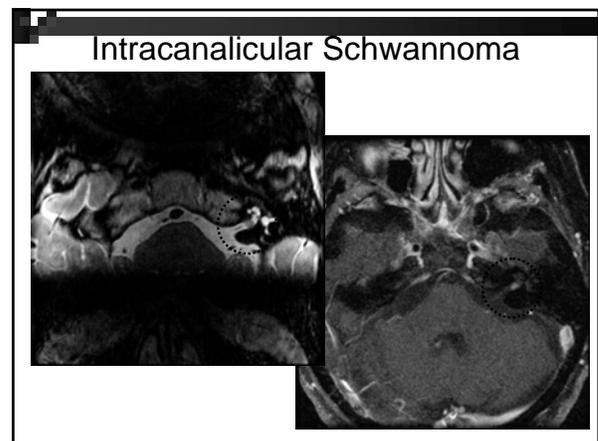
NOT Astrocytoma }

NOT Optic Glioma }

NIH Diagnostic Criteria.

NF-2 Requires one or more items

- Bilateral 8th nerve Masses
- Relative with NF-2 and either:
 - Unilateral 8th nerve Mass
 - Any Two:
 - "Neurofibroma", Meningioma, Glioma, Schwannoma, (Congenital) Lens Opacity



Bilateral Vestibular Schwannoma



From Laszlo Mechtler, DNI

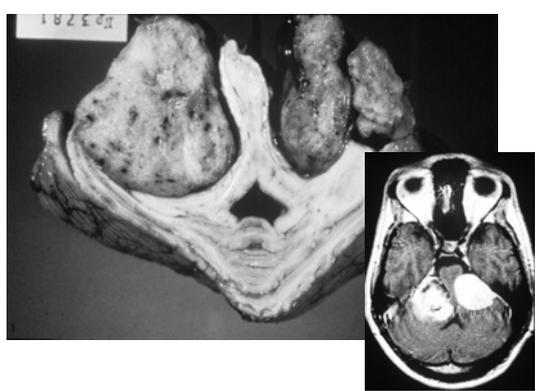
SCHWANNOMA

- 5-10% of All CNS Tumors
- Benign, Slowly growing
- F > M (Intracranial), M > F (Spinal)
- 30's - 60's, w/NF-2 10's - 30's
- Sensory Nerves (usually):
 - CNN VIII (Sup. Vestibular), V, X
 - Spine: Dorsal Roots
- Majority (>90%) are Sporadic
- Multiple in NF-2, Bilat. VIII Pathognomonic

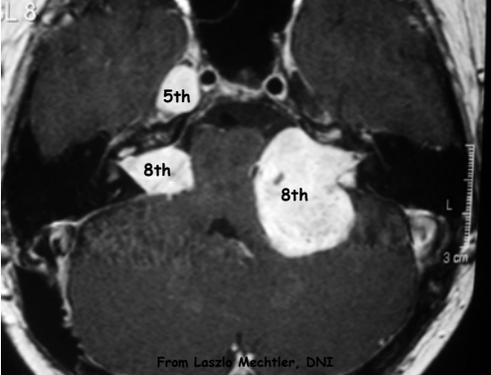
Bilateral Vestibular Schwannoma



Bilateral Vestibular Schwannoma



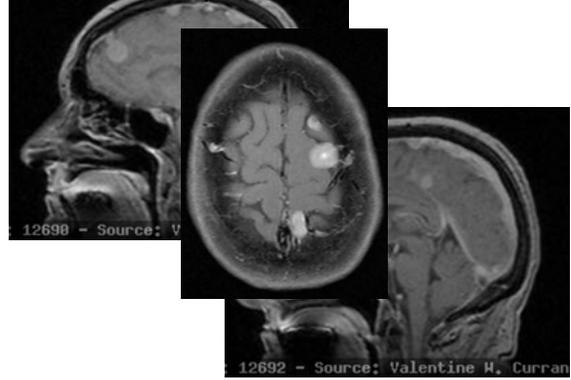
Bilateral vestibular and one Trigeminal Schwannoma



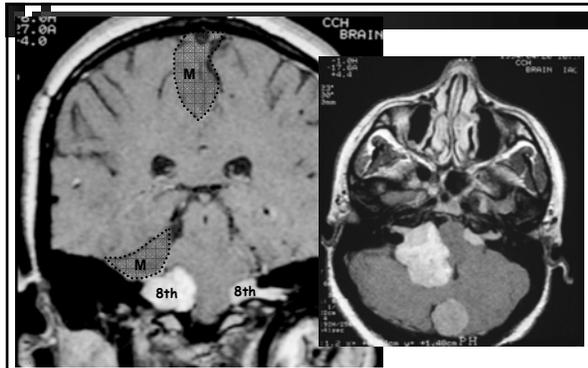
axial

From Laszlo Mechtler, DNI

Multiple Schwannomas



12692 - Source: Valentine M. Curran



Multiple Schwannomas and Meningiomas

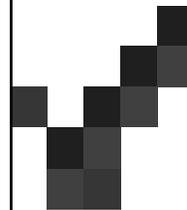


Multiple Inherited Schwannomas, Meningiomas, and Ependymomas

Neurofibromatosis Type 1
Chromosome 17q
neurofibromin

vs.

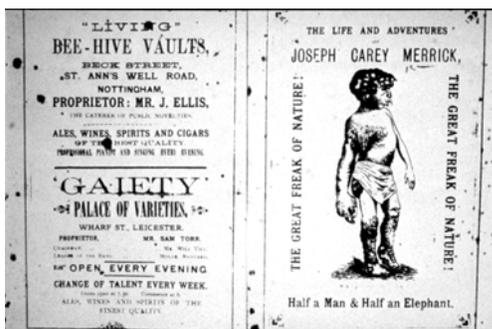
Neurofibromatosis Type 2
Chromosome 22q
neurofibromin2,
schwannomin, merlin



Neurofibromatosis Type 1
or
von Recklinghausen Disease

Chromosome 17
Proteins: pNF (neurofibromin)

The Original Elephant Man



Proteus Syndrome "Elephant Man"



The Elephant Man Had Proteus Syndrome

NEW STUDY SHOWS 'ELEPHANT MAN' HAD PROTEUS SYNDROME

Joseph C. Merrill, MD, has been the subject of many studies to diagnose the exact cause of his disease since 1988. It is a genetically inherited condition called Proteus Syndrome, which is a rare condition of the body's connective tissue. Merrill's condition caused him to have a large, elephant-like head and trunk. Merrill actually had Proteus syndrome rather than neurofibromatosis, as was previously believed.

Proteus syndrome is an extremely rare disorder that was first recognized during Merrill's life. Over the last 100 years, a number of diagnoses have been suggested as the cause of Merrill's disease, including neurofibromatosis, but Merrill's condition, Proteus Syndrome, was finally confirmed.

In the new research, Dr. Merrill and colleagues performed radiographic and genetic analysis to identify the cause of Merrill's condition. The Proteus syndrome, which was first described in 1920, is a rare condition that has been reported to show most of the radiological and clinical features seen in neurofibromatosis and proteus syndrome, but without the characteristic skin lesions.

Call Overgrowth
Merrick and Proteus syndrome have a condition that will grow that causes overgrowth of soft tissue over other body tissues. The disease was first recognized until 20 years ago. Since then, there has been some controversy over whether it is a genetically inherited condition. It is not considered an inherited disease but thought to be caused by a gene mutation.

The genetic status of the head showed bone overgrowth associated with neurofibromatosis and overgrowth of the skin and hair on the right side of the face. The study also showed that the skull of the 'Elephant Man' had a large, elephant-like head and trunk. The study also showed that the skull of the 'Elephant Man' had a large, elephant-like head and trunk. The study also showed that the skull of the 'Elephant Man' had a large, elephant-like head and trunk.

CT scans of the skull of Joseph Merrick, Victorian England's famous "Elephant Man," show dramatic overgrowth of bone on the right side of the skull. Merrick's head measured 20 inches in circumference, compared with 14 inches for a normal man. CT scans courtesy of The Royal London Hospital.

NIH Diagnostic Criteria: NF-1 Requires two items

- Cafe-Au-Lait spots
 - 6 or more
 - 5 mm child, 15 mm adult
- Neurofibromas - 2 or more
- Plexiform Neurofibroma - 1
- Axillary (Intertriginous) Freckling - 1
- Optic Glioma
- Lisch Nodules (Iris) - 2 or more
- "Distinctive Bone Lesions"
- 1st degree Relative with NF-1

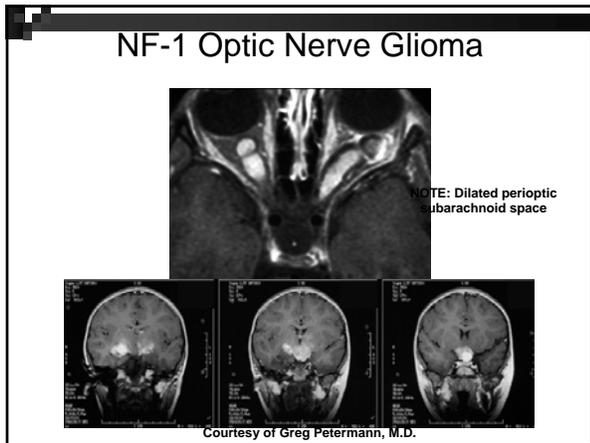
NF-1: EYE MANIFESTATIONS

- **LISCH Nodules (Iris Hamartomas)**
 - Penetrance > 90%
 - Specificity > 90%
 - Translucent/pigmented
 - Small (< 3mm.), Slit-Lamp Exam
- **OPTIC GLIOMA**
 - Up to 15% of patients
 - Pilocytic Astrocytomas
 - Benign ("Hamartoma-like"), Tx?
 - True Neoplasms, spread along SAS
 - up to 1/2 of Childhood ONG w/NF-1

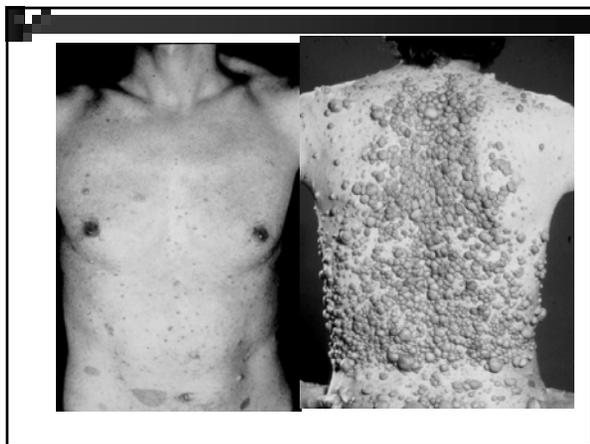
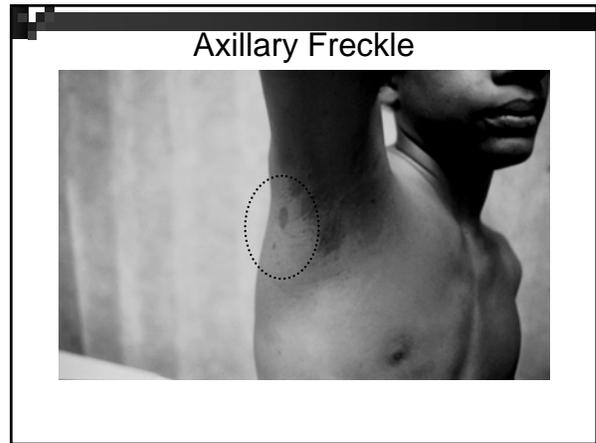
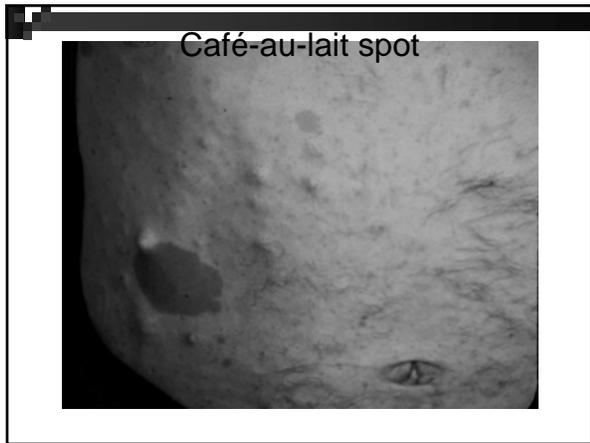
Lisch Nodules

Optic Nerve Glioma

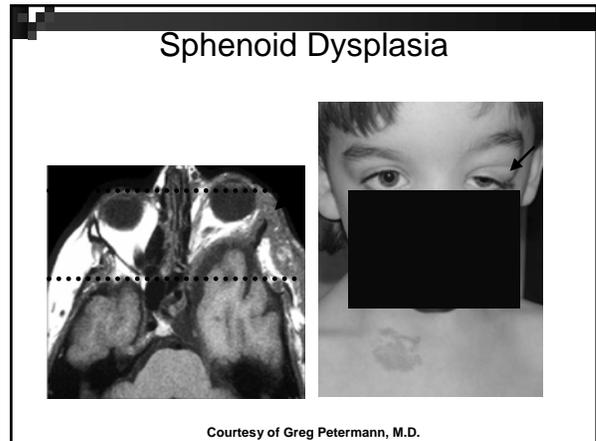
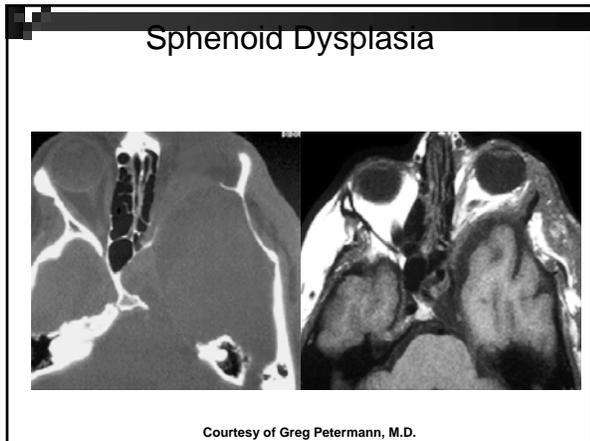
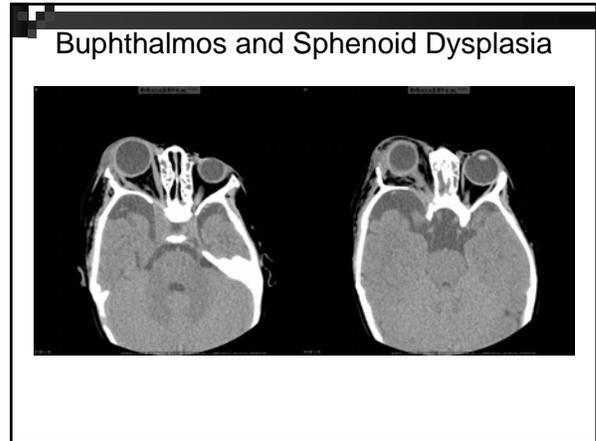
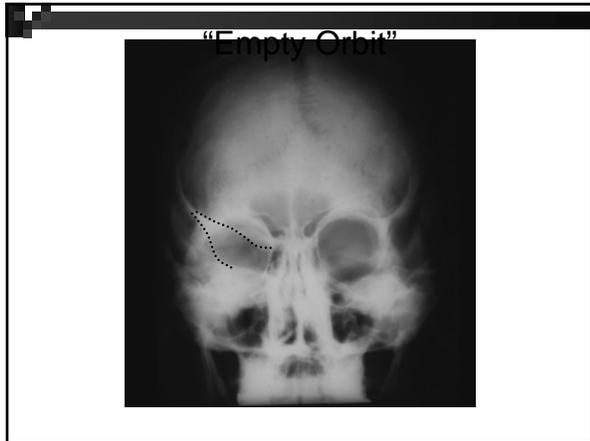
NF-1 Optic Nerve Glioma



- ### NEUROFIBROMATOSIS - 1
- Cutaneous Manifestations
 - **Cafe-au-Lait spots**
 - Intertriginous Freckling
 - **Neurofibromas (Skin and SubQ)**
 - Fibroma Molluscum (TNTC NFB)
 - Elephantiasis Neuromatosa
 - diffuse skin thickening/plexiform NFB
 - -or- focal gigantism

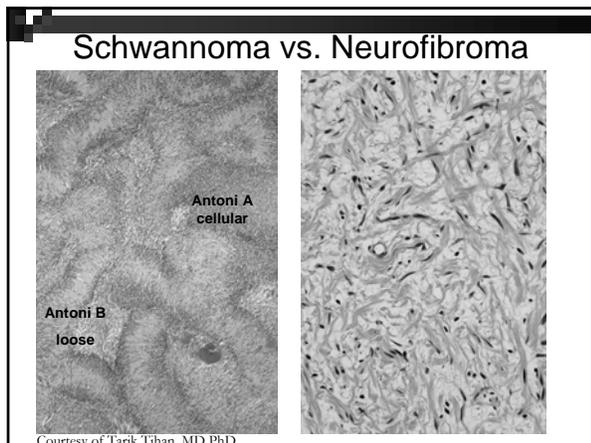


- ### NEUROFIBROMATOSIS - 1
- Bone Dysplasia and Remodeling
 - Macrocephaly
 - **Craniofacial dysplasia**
 - Especially sphenoid
 - **Vertebrae** (scalloping, scoliosis)
 - **Pseudoarthrosis**
 - especially congenital
 - Genu Valgum/Varum
 - Twisted "Ribbon Ribs"



- NERVE SHEATH TUMORS**
- **Schwannoma (Sporadic >> NF-2 > NF-1)**
 - focal mass, eccentric to nerve
 - usually sensory root, cranial and spinal nerves
 - **Neurofibroma**
 - usually NF-1, esp. if spinal or paraspinal
 - fusiform, spindle, or dumb-bell lesion
 - **Plexiform Neurofibroma (usually NF-1)**
 - diffuse or fusiform enlargement
 - **Malignant Peripheral Nerve Sheath Tumor**
 - NF-1 or Sporadic

- Neurofibroma vs. Schwannoma**
- | | |
|--|--|
| <ul style="list-style-type: none"> ■ Neurofibroma <ul style="list-style-type: none"> □ Schwann cells □ Fibroblasts □ Acellular material □ Infiltrating □ Resect Parent Nerve | <ul style="list-style-type: none"> ■ Schwannoma <ul style="list-style-type: none"> □ Schwann Cell Neoplasm □ Secondary vascular changes □ Mostly cellular □ Encapsulated □ Nerve Sparing Surgery |
|--|--|



- ### Distribution of Nerve Sheath Tumors
- **Intra-Cranial => Schwannoma**
 - Sporadic >> NF-2
 - Spinal => Both Types (S >> N)
 - Dumbbell => Both (N >> S)
 - PNS => Both
 - **Cutaneous => Neurofibroma**
 - Usually N in NF-1

- ### Neurofibromatosis: Spine
- **Neurofibroma (NF-1)**
 - Osteoporosis (NF-1, only?)
 - Idiopathic
 - Parathyroid Adenoma
 - **Schwannoma**
 - **Meningioma**
 - **Ependymoma**
- } NF-2

- ### INTRASPINAL NEOPLASMS
- 68 Patients with 86 Spinal Nerve Sheath neoplasms
 - Sporadic tumors: 42 pts. (65%)
 - 46 Schwannomas
 - 40 Sporadic tumors
 - 6 in NF-2 patients
 - 16 Neurofibromas
 - 14 in NF-1 patients
 - 2 Sporadic tumors

- ### Neurofibromatosis : Spine
- Scoliosis (NF-1, only?)
 - Simple ("idiopathic")
 - **Acute Cervical Kyphosis**
 - Dural Ectasia (NF-1, only?)
 - Vertebral Scalloping
 - Arachnoid "cysts"
 - **Lateral Thoracic meningocele**



Enlarged Neural Foramen



DDx:

- Nerve Sheath Tumor
 - Neurofibroma
 - Schwannoma
- Arachnoid Cyst
- Bone Dysplasia

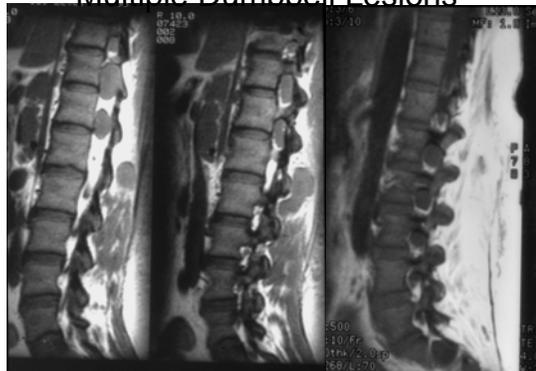
Neurofibromatosis: Enlarged Neural Foramen

- Nerve Sheath Tumor
 - Neurofibroma
 - NF-1 >> sporadic
 - "dumbbell" shape
 - Schwannoma
 - sporadic >> NF-2
- Mesodermal Defect
 - NF-1 only?
 - Dural weakness
 - Bone weakness

Enlarged Neural Foramen



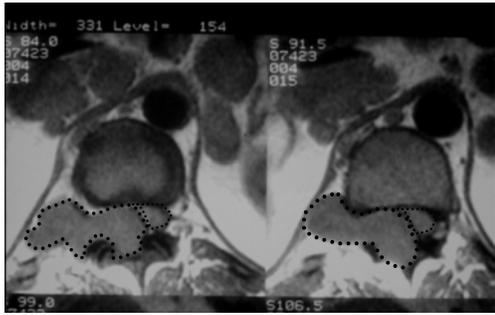
Multiple Dumbbell Lesions



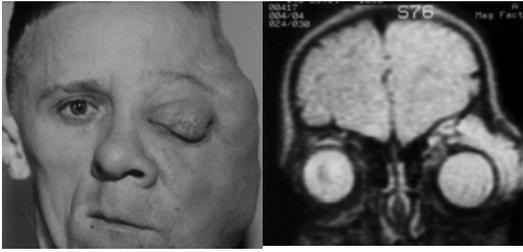
Multiple Dumbbell Lesions



Dumbbell Neurofibroma

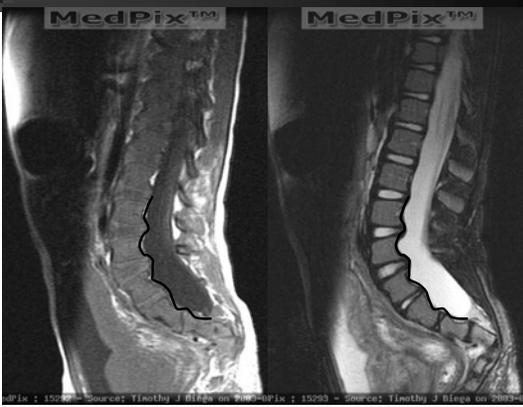


Plexiform NF

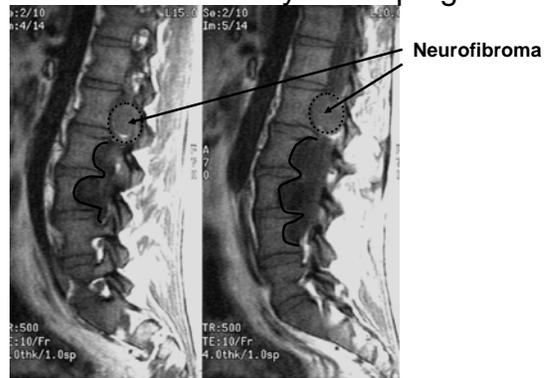


NEUROFIBROMATOSIS-1: Spine

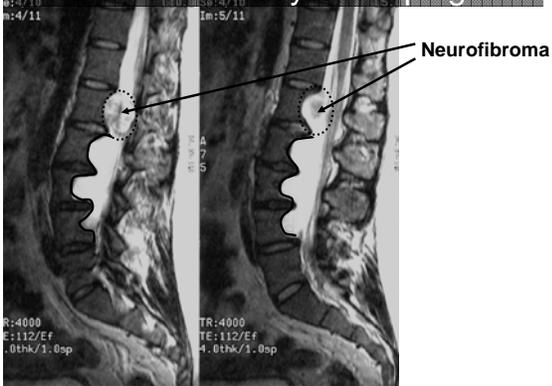
- Scoliosis (Acute Cx Kyphoscoliosis)
- Vertebral Scalloping
- Enlarged Neural Foramina
- Lateral Thoracic Meningocele



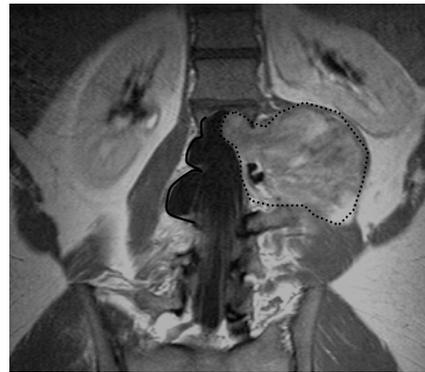
Vertebral Body Scalloping



Vertebral Body Scalloping



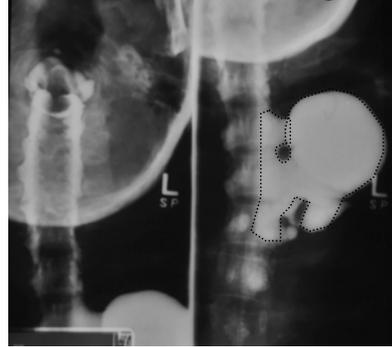
Arachnoid Cyst & Neurofibroma



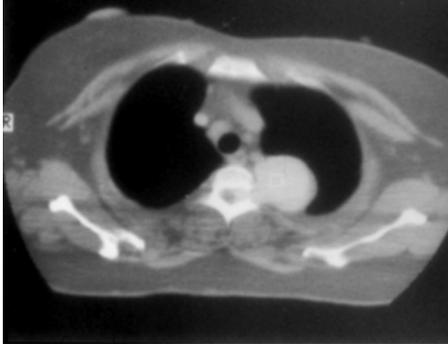
NEUROFIBROMATOSIS-1

- Posterior Meningocele (sporadic)
 - dorsal dysraphism, closure of tube
- Anterior Meningocele (sporadic)
 - neurenteric canal/cyst
 - anterior vertebral cleft
- Lateral Thoracic Meningocele (NF-1)
 - "pulsion diverticulum" of SAS
 - negative intrathoracic pressure
 - no overlying paravertebral MM.

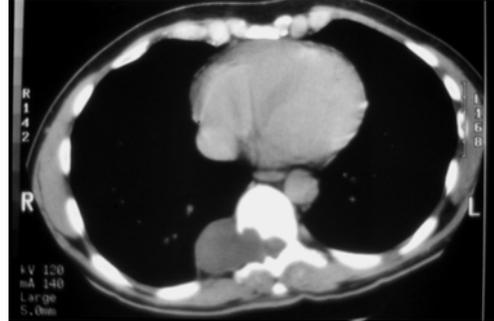
Lateral Thoracic Meningocele



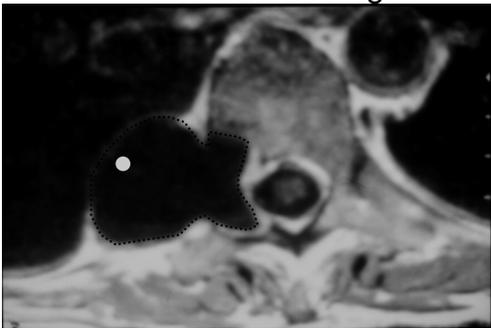
Lateral Thoracic Meningocele



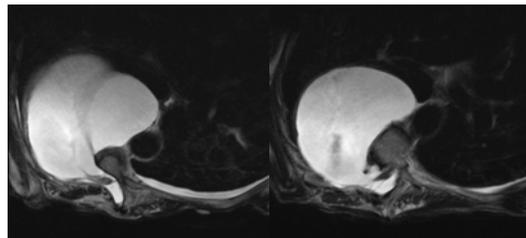
Lateral Thoracic Meningocele



Lateral Thoracic Meningocele



Lateral thoracic meningocele in NF-1



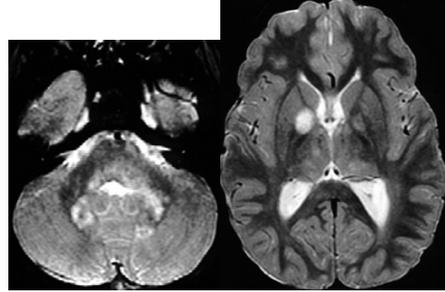
Courtesy Mauricio Castillo, M.D. UNC

NEUROFIBROMATOSIS - 1: DBO's MR Signal Abnormalities

- **T1W Bright Foci**
 - globus pallidus
- **T2W Bright Foci**
 - w/o mass, don't enhance
 - Cerebellar peduncles, Pons, midbrain
 - globus pallidus, thalamus, optic radiations
- **What in the heck are they??**
 - Ectopic Schwann cells, Melanocytes ??
 - Dysmyelination ??
 - intracellular proteinaceous fluid ?

**Deep Bright
Objects**

High signal in Brain on T2 Resolves as patients age

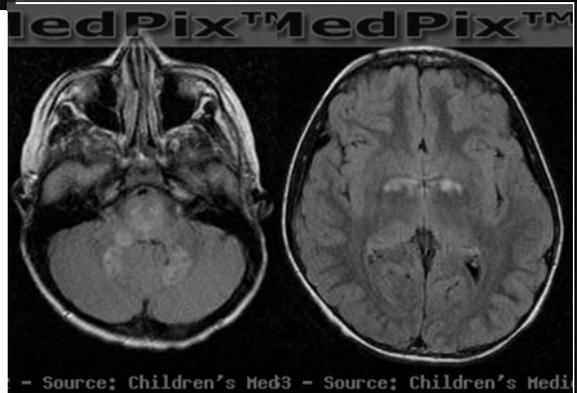


Courtesy of Greg Petermann, M.D.

DBO's and NF-1

- **Incidence:** A considerable body of knowledge suggests that these Deep Bright Objects or DBO's are very common in children with NF-1 (>90% in some series).
- **Age:** They are **most frequent** from 4 - 12 years of age. They are uncommon under the age of 4, and begin to **fade away** after the age of 16.
- **Location:**
 - Globus Pallidus - 30%
 - Cerebellum - 23%
 - Midbrain - 16%

**Deep
Bright
Objects**

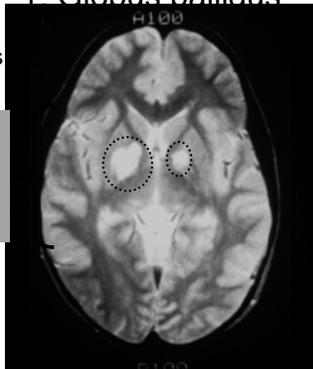


- Source: Children's Med3 - Source: Children's Medi

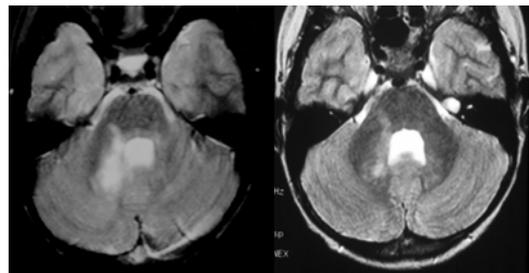
DBO's of NF-1: Globus pallidus

- Neurofibromatosis
- Objects

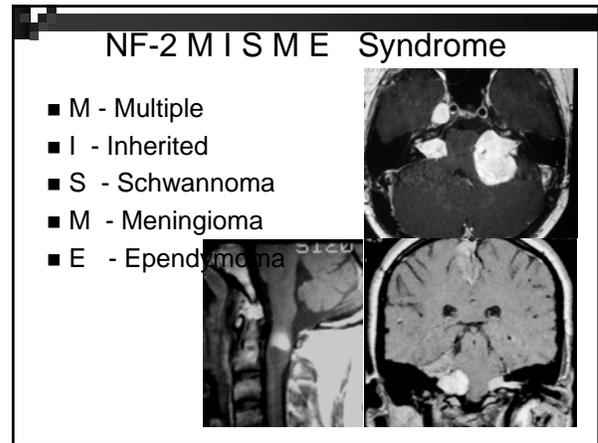
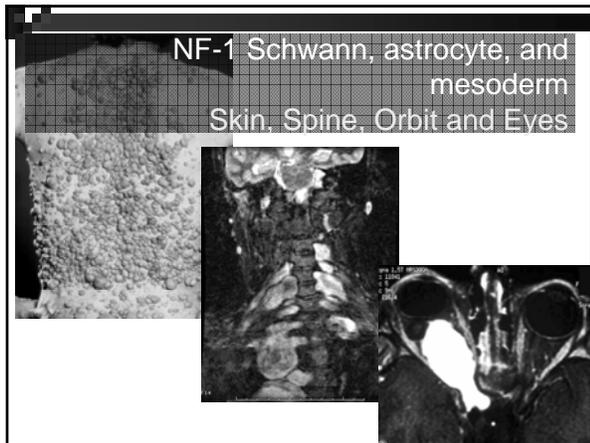
**Deep
Bright
Objects**



DBO's of NF-1: Cerebellar peduncle



Early ----- Later



Go Raimh Maith Agat
Thank You!
 Muito Obrigado
EUXAPIΣΤΩ !
 Mahalo !
 Dank u wel !
Merci Beaucoup
 Danke Schön !
 Mil Gracias